Review Article

Diagnosis of anemia in pregnancy

Ahmad Al-Khaffaf, Francesco Frattini, Roberta Gaiardoni, Elda Mimiola, Cinzia Sissa, Massimo Franchini

Department of Hematology and Transfusion Medicine, Carlo Poma Hospital, Mantua, Italy

Contributions: (I) Conception and design: A Al-Khaffaf, M Franchini; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Massimo Franchini, MD. Department of Hematology and Transfusion Medicine, Carlo Poma Hospital, Mantua, Italy.
Email: massimo.franchini@asst-mantova.it.

Abstract: Anemia in pregnancy is a worldwide health and social problem. While some degree of dilutional anemia is very frequent and can be considered part of the normal physiology of pregnancy, iron deficiency anemia is likewise common during pregnancy but can have serious adverse health consequences for the mother and child. Thus, it is mandatory to perform a prompt diagnosis of iron deficiency anemia distinguishing it from physiologic anemia, as well as to identify other less common causes of anemia that may require treatment. In this narrative review, we summarize the main diagnostic, clinical and therapeutic characteristics of the most important types of anemia during pregnancy.

Keywords: Anemia; pregnancy; iron deficiency; sickle cell anemia, diagnosis

Received: 07 November 2019; Accepted: 06 December 2019; Published: 20 January 2020.
doi: 10.21037/jlpm.2019.12.03
View this article at: http://dx.doi.org/10.21037/jlpm.2019.12.03

Introduction

During normal pregnancy, the plasma volume expands by 40–60%, whereas the red blood cell mass expands by 20–50%. Thus, a physiologic anemia ("dilutiomal anemia") develops, leading to a normal hematocrit value of 30–32%. Hemoglobin levels lower than 10 g/dL suggest the possibility of a pathologic process, such as nutritional deficiency. The prevalence of anemia in pregnancy increases from 8% in the first trimester to 12% and 34% in the second and third trimester (1). At present, there is no definitive evidence whether the hemoglobin threshold for transfusion should be 7 or 8 g/dL, although some studies indicate greater risk of intrauterine growth restriction (IUGR) and adverse effects on fetal growth when the hemoglobin falls below 8 g/dL (2). In this narrative review, we summarize the current evidence on the main diagnostic, clinical and therapeutic aspects of the most and less common types of anemia during pregnancy.

Iron deficiency anemia

Iron deficiency accounts for 75% of cases of non-physiologic anemia in pregnancy, and the incidence of iron deficiency anemia during pregnancy world-wide is about 41.8% (3). The laboratory diagnosis of iron deficiency anemia is based on a complete cell blood count. Additional tests include the determination of the levels of serum ferritin, iron, total iron-binding capacity, and/or transferrin. In an individual who is anemic from iron deficiency, these tests usually show the following results: low hemoglobin and hematocrit, low mean cellular volume, low serum ferritin levels, low serum iron, high transferrin or total iron-binding capacity and low iron saturation. The peripheral smear or blood slide may show small, oval-shaped cells with pale centers. In addition, in severe iron deficiency, the white blood count may be low and the platelet count may be high or low (1). *Table 1* summarizes the main laboratory characteristics of iron deficiency anemia along with the

Table 1 Differential diagnosis of pregnancy-related anemias

Parameter	Iron deficiency anemia	Megaloblastic anemia	Microangiopathic hemolytic anemias	Aplastic anemia	Sickle cell anemia
Hemoglobin	↓	↓	↓	↓	↓/↓↓
Hematocrit	↓	↓	↓	↓	↓
RBC count	↓	↓	↓	↓	↓
MCV	↓↓	↑↑	N	N/↑	N/↓
MCHC (mean cell hemoglobin concentration)	↓	↓	N	N	N/↓
RDW (red cell distribution width)	↑	↑	↑	↑	↑
Reticulocytes	↓/N	↓/N	↑↑	↓	↑
Ferritin	↓	N/↑	–	–	–
Transferrin	↑	–	–	–	–
Transferrin saturation	↓	–	–	–	–
TIBC (total iron binding capacity)	↑/N	–	–	–	–
Serum Iron	↓	N/↑	–	–	–
Serum B12	–	↓/N	–	N/↑	–
Serum Folate	–	↓/N	–	N/↑	–
Eritro-morphology	Hypochromic RBCs	Macrocytic RBCs, Howell-Jolly bodies	Schistocytes, RBCs fragmentation	Unremarkable	Sickle cells, target cells, Howell-Jolly bodies
White blood count	N/↓	↓/N	N/↓	↓	–
Platelet count	N/↓	↓/N	↓↓	↓	–
LDH	–	↑	↑↑	N/↑	↑/N
Bilirubin	–	N/↑	↑↑	–	↑/N
Haptoglobin	–	N/↑	↑↑	–	N/↑
Hemoglobin electrophoresis	–	–	–	–	↑HbS, ↓HbA, ↑HbF

differential diagnosis with the other pregnancy-related anemias.

Clinical manifestations of iron deficiency include fatigue, tachycardia, dyspepsia, poor exercise tolerance, and suboptimal work performance. In addition, iron deficiency is associated with postpartum depression, poor maternal infant behavioral interaction, impaired lactation, low birth weight, premature delivery, IUGR, and increased fetal and neonatal mortality. The total iron requirement during pregnancy is 1,190 mg, and, with a net iron balance during pregnancy of 580 mg, this equates to a requirement of 2 mg daily (4). Besides poor nutrition, other factors impairing iron absorption include antacids and micronutrient deficiencies, including vitamin A, vitamin C, zinc, and copper deficiency. In the absence of iron supplementation, hemoglobin falls to 10.5 g/dL at 27–30 weeks of gestation; with iron supplementation, the nadir is less severe, 11.5 g/dL. By the third trimester, serum ferritin declines, erythropoietin levels surge, and maternal hepcidin levels are reduced to facilitate iron transfer and use at delivery (5).

Current recommendations suggest that pregnant patients receive 15-30 mg daily of supplemental elemental iron, although studies examining the efficacy of iron supplementation during pregnancy have not shown a clear

benefit to pregnancy outcomes (6,7). Ferrous gluconate is better tolerated due to fewer gastrointestinal effects than ferrous sulfate. For patients who do not tolerate oral iron, parenteral iron may be used. Iron sucrose is categorized as pregnancy class B (presumed safe based on animal models) and is preferred over iron dextran or iron (fumoxytol), which are considered pregnancy class C (safety uncertain) (8). Data about the use of ferric carboxymaltose administration in the second and third trimester of pregnancy is likely to be safe and effective with correction of anemia before delivery and prevention of significant post-partum anemia (9). Alternative causes of anemia should be sought in patients refractory to standard iron therapy. Finally, although iron supplementation improves hematologic parameters, it may not improve neonatal outcomes (7). In conclusion, for the management of pregnant women, daily 15–30 mg elemental iron is recommended. For those not able to tolerate oral iron, parenteral iron is preferred, but it could be considered safe from the second trimester.

Megaloblastic anemia

The majority of macrocytic anemias during pregnancy, prior to mandatory folate fortification programs, where due to folate deficiency, whereas vitamin B12 deficiency is rare. The diagnostic approach to megaloblastic anemia involves the morphological and laboratory (increased mean cellular volume) recognition of megaloblastosis and the identification of the specific vitamin deficiency, i.e., the assay of serum vitamin B12 and folic acid levels. Multivitamin and folic acid supplementation reduce placental abruption and recurrent pregnancy loss. Folate requirements increase from 50 µg daily in the non-pregnant female to at least 150 µg daily during pregnancy, and the Centers for Disease Control and Prevention (CDC) recommend supplementation with 400 µg daily of folate to prevent neural tube defects (10). Folate deficiency is most precisely diagnosed by measuring plasma levels of homocysteine and methylmalonic acid. For the management of pregnant women, daily folic acid 400 µg is recommended (11-13).

Microangiopathic hemolytic anemias

Microangiopathic hemolytic anemias are disorders characterized by hemolytic anemia in association with thrombocytopenia and multi-organ failure. Hemolysis is caused by microthrombi in small capillaries and is characterized by schistocytes, elevated lactate dehydrogenase (LDH) and elevated indirect bilirubin, and reduced haptoglobin. Although they represent an uncommon cause of anemia in pregnancy, they may have devastating consequences for both the pregnant mother and child. These disorders, including thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), preeclampsia, and hemolysis, elevated liver function tests, low platelets (HELLP), are challenging to diagnose, given the wide overlap in clinical presentation. Moreover, they are difficult to treat, given disparate treatments (14,15). The mainstay therapy for TTP and complement mediated HUS which usually occur in the third trimester and post-partum respectively, is the plasma-exchange. For the other pregnancy-related thrombotic microangiopathies (HELLP and preeclampsia) occurring in the third trimester, delivery is the mainstay of treatment (16).

Aplastic anemia

Aplastic anemia is a rare syndrome of bone marrow failure characterized by peripheral pancytopenia and marrow hypoplasia. Although the anemia is often normocytic, mild macrocytosis can also be observed in association with stress erythropoiesis and elevated fetal hemoglobin levels (8). Aplastic anemia is rare in pregnancy. It may be either associated with or precipitated by pregnancy. Some cases may either mimic or occur with idiopathic thrombocytopenia (ITP). The mechanism of the bone marrow aplasia that occurs in pregnancy is believed to be through the erythropoietic suppressor effects of hormones during pregnancy. Alternatively, preexisting aplasia may be uncovered during pregnancy (8). The diagnosis of aplastic anemia during pregnancy is associated with significant fetal, neonatal, and maternal morbidity and mortality (17). A causal relationship between pregnancy and aplastic anemia has not been conclusively established (18). Aplastic anemia may lead to maternal death in up to 50% of cases, usually caused by hemorrhage or infection, and in utero fetal complications may occur in one-third.

Hematopoietic bone marrow transplantation, albeit associated with significant 5-year survival rates in non-pregnant patients (19), is contraindicated in pregnancy, due to teratogenicity associated with pre-transplant immunosuppressant agents (20). Termination of pregnancy in order to perform hematopoietic stem cell transplantation is not usually recommended, because of the relatively favorable prognosis for mother and fetus when medical therapy is optimally used (21). For the management

of pregnant women with aplastic anemia, transfusions to maintain a hemoglobin 7–8 g/dL, a platelet count of >10,000/μL, and growth factors (e.g., G-CSF), as needed, are recommended. In pregnancy-induced aplastic anemia, the role of termination or early delivery should be considered in management: case reports indicate improvement of aplastic anemia following pregnancy (8).

Sickle cell anemia

Sickle cell anemia (SCA) is an inherited blood disorder caused by a mutation in the sixth amino acid of the β-globin gene and is characterized by an abnormality in the oxygen-carrying protein hemoglobin, leading to a rigid sickle-like red blood cell shape (22). The diagnosis is based on the detection of low red blood cell count (anemia) and of hemoglobin S at hemoglobin electrophoresis.

It is well established that pregnancy in women with SCA is high-risk related to underlying hemolytic anemia and multiorgan dysfunction. In non-pregnant women, less severe clinical forms such as SC hemoglobinopathy and S/β^+-thalassemia co-inheritance may pass unnoticed for these individuals are usually asymptomatic or oligosymptomatic and have hemoglobin concentrations near to or within the normal range. During pregnancy, however, these women may undergo complications as severe as those associated with the hemoglobin SS genotype (22,23). The physiological adaptations that occur in the circulatory, hematologic, renal and pulmonary systems during pregnancy can overburden organs that already have chronic injuries secondary to SCA, increasing the rate of obstetric complications like eclampsia and pre-eclampsia, worsening of vaso-occlusive crises and acute chest syndromes. Though pregnancy in SCA carries a higher risk of maternal and fetal complications, it can be managed by ensuring adequate perinatal care (24).

Thus, the major adverse events that can occur in patients with SCA need a particular management when regard pregnant women. For instance, pregnant women presenting with vaso-occlusive crises should be hospitalized, adequate bed rest and fluid intake should be ensured. For pain relief, paracetamol and other nonsteroidal anti-inflammatory agents should be given. If pain is not relieved narcotic analgesics may be used. However, meperidine should be avoided because of associated toxicity and risk of convulsions (25). The treatment of acute chest pain includes appropriate antibiotics, oxygen support, hydration, analgesics and if required blood transfusion (25). In addition, women presenting with chest pain and respiratory distress with normal chest X-ray should be suspected to have pulmonary embolism. Treatment should be started with low molecular weight heparins awaiting the confirmation of the diagnosis (25).

Pertaining to the hematological aspects, anemia is the most common complication of pregnancy in women with sickle cell disease. Blood loss, bone marrow suppression by parvovirus infection and nutritional deficiencies are the causes (26). Prophylactic red blood cell transfusion is done in some centers as it is believed that the risk of complications like stroke and acute coronary syndrome is decreased. However, the recent guidelines from the Royal College of Obstetrician and Gynecologists do not recommend the same. Transfusions are only indicated when Hb <7 g/dL because such low hemoglobin leads to decreased fetal oxygenation and abnormal fetal outcomes (25). HELLP syndrome can develop in up to 10% of women with pre-eclampsia. It can be managed conservatively or by urgent delivery depending on gestational age.

Conclusions

Anemia is the most frequent blood disorder occurring during pregnancy. Although a prompt identification is needed, the correct diagnosis is also important for an effective management for better maternal and neonatal outcomes (27,28).

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Giuseppe Lippi, Martina Montagnana and Zhi-De Hu) for the series "Laboratory Medicine in Pregnancy" published in *Journal of Laboratory and Precision Medicine*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jlpm.2019.12.03). The series "Laboratory Medicine in Pregnancy" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

References

1. Scholl TO. Iron status during pregnancy: setting the stage for mother and infant. Am J Clin Nutr 2005;81:1218S-22S.
2. Kozuki N, Lee AC, Katz J; Child Health Epidemiology Reference Group. Moderate to severe, but not mild, maternal anemia is associated with increased risk of small-for-gestational-age outcomes. J Nutr 2012;142:358-62.
3. Horowitz KM, Ingardia CJ, Borgida AF. Anemia in pregnancy. Clin Lab Med 2013;33:281-91.
4. Bothwell TH. Iron requirements in pregnancy and strategies to meet them. Am J Clin Nutr 2000;72:257S-64S.
5. Bah A, Pasricha SR, Jallow MW, et al. Serum Hepcidin Concentrations Decline during Pregnancy and May Identify Iron Deficiency: Analysis of a Longitudinal Pregnancy Cohort in The Gambia. J Nutr 2017;147:1131-7.
6. Elstrott B, Khan L, Olson S, et al. The role of iron repletion in adult iron deficiency anemia and other diseases. Eur J Haematol 2019. [Epub ahead of print].
7. Iqbal S, Ekmekcioglu C. Maternal and neonatal outcomes related to iron supplementation or iron status: a summary of meta-analyses. J Matern Fetal Neonatal Med 2019;32:1528-40.
8. Goonewardene M, Shehata M, Hamad A. Anaemia in pregnancy. Best Pract Res Clin Obstet Gynaecol 2012;26:3-24.
9. Froessler B, Collingwood J, Hodyl NA, et al. Intravenous ferriccarboxymaltose for anaemia in pregnancy. BMC Pregnancy Childbirth 2014;14:115.
10. Roy NBA, Pavord S. The management of anaemia and haematinic deficiencies in pregnancy and post-partum. Transfus Med 2018;28:107-16.
11. Sifakis S, Pharmakides G. Anemia in pregnancy. Ann N Y Acad Sci 2000;900:125-36.
12. Savage D, Gangaidzo I, Lindenbaum J, et al. Vitamin B12 deficiency is the primary causeof megaloblastic anaemia in Zimbabwe. Br J Haematol 1994;86:844-50.
13. Achebe MM, Gafter-Gvili A. How I treat anemia in pregnancy: iron, cobalamin, and folate. Blood 2017;129:940-9.
14. McMinn JR, George JN. Evaluation of women with clinically suspected thrombotic thrombocytopenic purpura-hemolytic uremic syndrome during pregnancy. J Clin Apher 2001;16:202-9.
15. George JN. The association of pregnancy with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Curr Opin Hematol 2003;10:339-44.
16. Neave L, Scully M. Microangiopathic hemolytic anemia in pregnancy. Transfus Med Rev 2018;32:230-6.
17. Deka D, Malhotra N, Sinha A, et al. Pregnancy associated aplastic anemia: maternal and fetal outcome. J Obstet Gynaecol Res 2003;29:67-72.
18. Rathore S, Pramanick A, Regi A, et al. Aplastic anemia in pregnancy. J Obstet Gynaecol India 2014;64:26-8.
19. Young ME, Potter V, Kulasekararaj AG, et al. Haematopoietic stem cell transplantation for acquired aplastic anaemia. Curr Opin Hematol 2013;20:515-20.
20. Aitchison RG, Marsh JC, Hows JM, et al. Pregnancy associated aplastic anaemia: a report of five cases and review of current management. Br J Haematol 1989;73:541-5.
21. Stibbe KJ, Wildschut HI, Lugtenburg PJ. Management of aplastic anemia in a woman during pregnancy: a case report. J Med Case Rep 2011;5:66.
22. Charache S, Scott J, Niebyl J, et al. Management of sickle cell disease in pregnant patients. Obstet Gynecol 1980;55:407-10.
23. Dickinson FT. Sickle-cell hemoglobin C disease in pregnancy: report of a case with review of the literature. J Am Osteopath Assoc 1980;79:591-4.
24. Jain D, Atmapoojya P, Colah R, et al. Sickle Cell Disease and Pregnancy. Mediterr J Hematol Infect Dis 2019;11:e2019040.
25. Boga C, Ozdogu H. Pregnancy and sickle cell disease: a review of the current literature. Crit Rev Oncol Hematol 2016;98:364-74.
26. Koshy M. Sickle cell disease and pregnancy. Blood Rev 1995;9:157-64.

27. Zdanowicz JA, Surbek D. Patient blood management in obstetrics - Review. Transfus Apher Sci 2019;58:412-5.
28. Muñoz M, Stensballe J, Ducloy-Bouthors AS, et al. Patient blood management in obstetrics: prevention and treatment of postpartum haemorrhage. A NATA consensus statement. Blood Transfus 2019;17:112-36.

doi: 10.21037/jlpm.2019.12.03
Cite this article as: Al-Khaffaf A, Frattini F, Gaiardoni R, Mimiola E, Sissa C, Franchini M. Diagnosis of anemia in pregnancy. J Lab Precis Med 2020;5:9.

